Regulatory Basis for U.S. Drug & Biologics Approval

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FDA Mission:

- FDA is responsible for:
  - Assurance of the Safety, Efficacy and Security of:
    - **Drug and Biological** products
    - Medical **Devices**
    - **Food** supply
    - **Cosmetics**
    - **Radiation products**
- FDA **does not** take into account cost or payment issues
- FDA **does not** regulate “practice of medicine”

Applicable FDA Centers for this Workshop:

Center for Drug Evaluation and Research (CDER)
•Drugs and Antibodies.
•Office of Hematology and Oncology Products

Center for Biologics Evaluation and Research (CBER)
•Cellular and Gene Therapies, Vaccines.

Center for Devices and Radiologic Health (CDRH)
•Devices, In Vitro Diagnostics, Diagnostic and Therapeutic Radiologics.

Combination Products

- Some products require reviews across Centers:
  - Photodynamic Therapy for Prostate Cancer
    - CDER-photosensitizing drug
    - CDRH-light source (optical fibers)
  - Office of Combination Products determines the center that will conduct the primary review
    - Normally, based on which component of the combination is responsible for the primary therapeutic effect
    - Example: Heat-activated cytotoxic drug activated by high-intensity ultrasound would likely be primarily reviewed in CDER with collaboration by CDRH.

Safety and Efficacy Requirements:

Drugs (FD&C Act) and Biologics (PHS Act)

- FD&C Act "Safe and Effective"
  - Adequate and well-controlled investigations (typically 2 or more trials)
  - Experts qualified to evaluate the effectiveness of the drug
  - Reach a conclusion that the drug will have the effect it purports
- PHS Act "Safe Pure and Potent"
  - FDA Modernization Act – Minimize differences in review and approval between drugs and biologics
- For all intents and purposes, Safety and Efficacy of Drugs and Biologics use a similar evidentiary framework

FDA Historical Perspective on Oncology Efficacy Endpoints

- 1970s, there were limited available therapies and tumor shrinkage (response rate) was accepted as a primary endpoint for approval

- 1980s, a change in this interpretation occurred:
  - Asymptomatic radiographic tumor shrinkage may not translate into an improvement in overall outcome (particularly given the toxicity of the cytotoxic agents being evaluated)

- Efficacy should be based on Direct Clinical Benefit
    - How one “Feels, Functions or Survives”

Categories of Efficacy Endpoints

- Direct Measure of Clinical Benefit
  - Overall Survival
  - Measures of symptoms or function
    - Patient Reported Outcomes
  - Decrease in morbid complications (Skeletal Related Events)

- Established Surrogates of Clinical Benefit
  - Substantial existing data and regulatory precedence increasing the certainty that the surrogate is predicting true clinical benefit
    - Dependent on Clinical Situation: DFS (adjuvant breast)

- Unestablished Surrogate of Clinical Benefit
  - Limited existing data, lack of regulatory precedence
    - Dependent on Clinical Situation: Response Rate (lung cancer).

  - Use of a serum/blood biomarker (e.g. PSA, CTC) as an efficacy endpoint is rare, and would require substantial supportive data

There are Two Approval Pathways for Drugs and Biologics in the U.S.

- Regular Approval
- Accelerated Approval

Regular Approval

- Regular approval requires
  - Substantial evidence of Safety and Efficacy
  - Well-controlled clinical trials (usually 2 or more)
  - based on **prolongation of life, a better life or an established surrogate for either of the above**

- Therefore, efficacy endpoints for Regular Approval may include:
  - Overall Survival (“Prolongation of life”)
  - Patient Reported Outcomes or SRE delay (“A better life”)
  - DFS in Breast Cancer (“Established Surrogates”)

- There is no comparative efficacy requirement for Regular Approval
  - Drug or Biologic must be shown to be safe and effective
  - (as effective as an alternative therapy for the same disease and indication)
  - Allows for non-inferiority

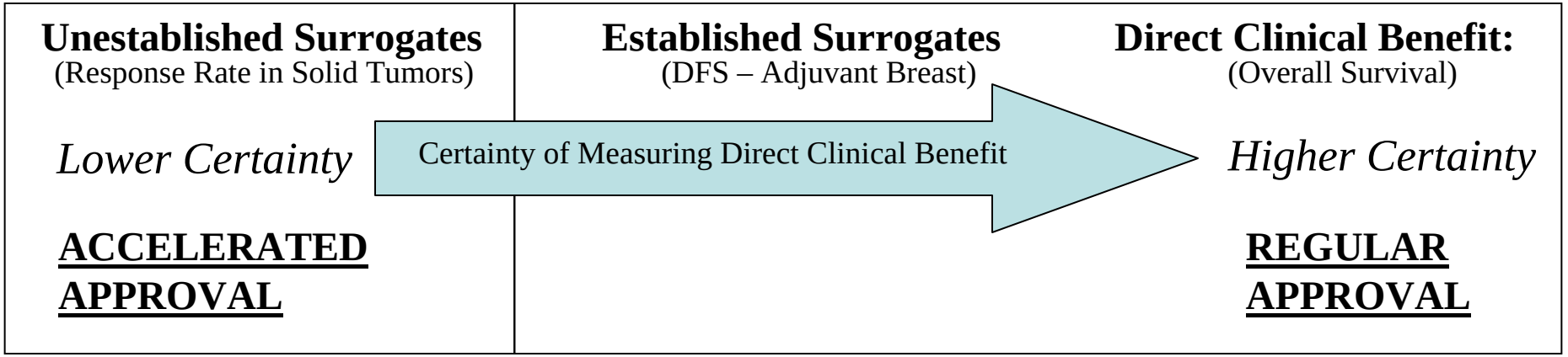
Accelerated Approval

- For products that treat "Serious or life-threatening diseases"
- "Provide meaningful therapeutic benefit… over existing therapies"
- *Can be based on a* ***"Surrogate endpoint… reasonably likely… to predict clinical benefit"***
- But are "Subject to the requirement that the applicant study the drug further"
- These Post-Marketing Clinical Trials are Required
  - Should usually be underway at the time of accelerated approval
  - Applicant should carry out studies with due diligence

Accelerated Approval

- There are Benefits and Risks to the Accelerated Approval Pathway
  - Benefits:
    - Use of an unestablished surrogate endpoint
    - Usually provides for earlier events and smaller, quicker trials
  - Risks:
    - Must demonstrate product is better than existing therapy
    - Must complete post-marketing trials and confirm meaningful clinical benefit
- 10% of Accelerated Approvals in oncology have been withdrawn for failure to confirm a benefit
  - We expect a small percentage of products to fail to verify this benefit
  - This is the tradeoff for earlier availability of promising anti-cancer agents.

Efficacy Endpoints and Approval Pathways



- The more uncertainty that exists that the endpoint measures direct clinical benefit, the more data that will be required to support approval:
  - Large magnitude of effect
  - Internal consistency via key secondary endpoints
  - Randomized Data
  - Supporting Clinical Trials
  - Confirmatory Post-Marketing Trials (Accelerated Approval)

Other Aspects of Efficacy Endpoints:

Susceptibility to Bias and Accuracy of Timing of the Event

- Overall Survival is the Gold Standard in Oncology
  - Interpretation of Event is not an issue (least prone to bias)
  - Event timing is known to the day
- Radiographic Time to Event (PFS, DFS, MFS)
  - Interpretation of the event requires investigator or independent review
  - Event timing is dependent on the frequency of radiographic assessments
- Time to Intervention (e.g. prostatectomy, prostate biopsy) has not been used for approval in prostate cancer and is problematic
  - While delay or avoidance altogether of major surgery may be considered a direct clinical benefit, there are significant concerns regarding the potential for bias (Investigator and Patient Decision Determines the Endpoint)
  - Mitigation of possible bias may include blinding, placebo or sham procedure and pre-defined objective triggers for intervention; however these may or may not be feasible

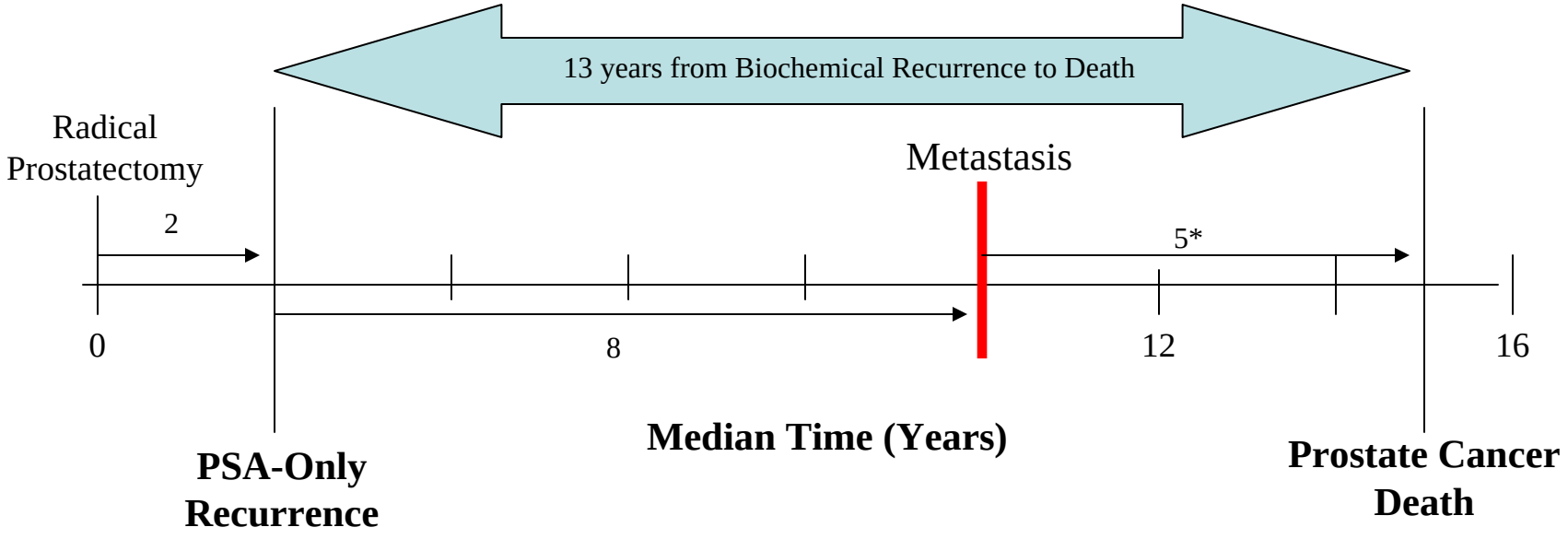
Life-Threatening Diseases:
Regulatory Flexibility in Oncology

- Safety:
  - Historically, acceptance of higher degrees of toxicity
- Efficacy:
  - Acceptance of a Single Trial rather than 2 or More Trials
    - For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.
  - Acceptance of alternative development strategies
    - Frequent use of the Accelerated Approval Pathway
    - Use of Surrogate Endpoints – Radiographic PFS, Response Rate
- Overall Risk:Benefit Determination for NDA or BLA Review
  - Takes into consideration more than just the safety and efficacy data
    - Available Therapy, Disease, Indication,, Regulatory Precedence, State of Science

The Challenge in Localized Prostate Cancer

- Drug approvals in the last 10 years have occurred in the metastatic CRPC setting
- The endpoints used for initial approval have been considered Direct Measures of Clinical Benefit
  - Overall survival
  - Skeletal related events
  - Pain composites
- The time to events considered direct measures of clinical benefit (survival, pain, SRE) is very long for localized prostate cancer

Using Direct Measures of Benefit Challenging Given the Long Time to Events

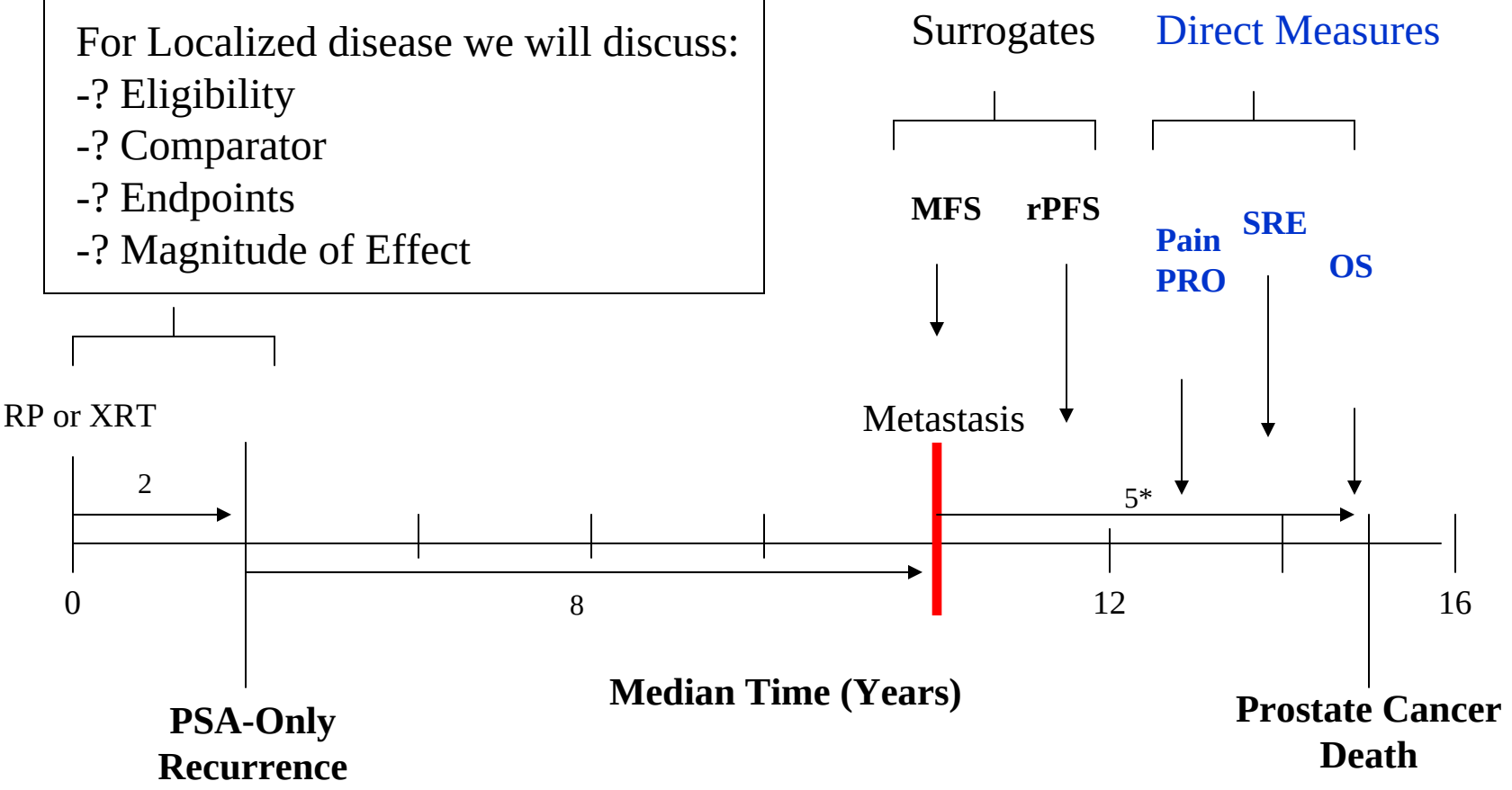


* 43% of those with metastasis had died. Median time to death was 5 years.

Based on Pound et al: JAMA 1999

Goals of the Local Therapy Workshop

For Localized disease we will discuss:
-? Eligibility
-? Comparator
-? Endpoints
-? Magnitude of Effect



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Summary

- There are many options for efficacy endpoints to describe clinical benefit, but uncertainty increases with the use of surrogate endpoints
- Increased uncertainty requires additional evidence that the surrogate endpoint predicts true clinical benefit
- Even when attempting to measure direct clinical benefit, bias must be addressed and mitigated
- Approval decision rests in using all data available to determine whether the drug or biologic provides clinically meaningful benefit to patients